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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/038,206	01/02/2002	Jasper Rine	UOCB118456	1317

26389 7590 07/31/2007

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ART UNIT	PAPER NUMBER
1631	

MAIL DATE	DELIVERY MODE
07/31/2007	PAPER

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/038,206
Filing Date: January 02, 2002
Appellant(s): RINE ET AL.

Tineka J. Quinton
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 16 April 2007 appealing from the Office action mailed 18August 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner. The rejection of claim 69 under 35 U.S.C. 101 has been withdrawn in view of the entry of the after final amendment filed on 15 February 2007.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5,800,992 Fodor et al. 09-1998

Gress et al. Hybridization fingerprinting of high-density cDNA-library arrays with cDNA pools derived from whole tissues. Mammalian Genome Vol. 3, pages 609-619 (1992)

Granelli-Piperno et al. Lymphokine and Nonlymphokine mRNA Levels In Stimulated Human T Cells. Journal of Experimental Medicine Vol. 163 pages 922-937 (1986)

Fodor et al. Light-Directed, Spatially Addressable Parallel Chemical Synthesis. Science Vol. 251 pages 767-773 (1991)

Watson et al. Molecular Biology of the Gene, Fourth Edition, the Benjamin/Cummings Publishing Company, Inc. Menlo Park, California, Chapter 18, pages 550-594 (1987)

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 38-53, 55-66, 68-83, and 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gress et al. in view of Granelli-Piperno et al. in view of either Fodor et al. '98 (U.S. Patent No. 5,800,992) or Fodor et al. '91 (reference 9 in the Information Disclosure Statement filed 20 November 2002).

The claims are drawn to a method of assay of the response of a living thing to a stimulus by use of an array of probes comprising a predetermined sequence of nucleotides to individual

gene transcripts by comparing databases comprising results of hybridizations of labeled polynucleotides derived from cells either treated with different stimuli or unstimulated control cells, the database produced by the method, and methods of generating the database produced by the method. The responses are measured by converting an output signal to an electrical signal and then converting the electrical signal to a value in a database. In some embodiments at least 50% of the gene transcripts of the cell are assayed, the cells are human cells, the probes consist of 24-240 nucleotides, and the database is computer implemented. In some embodiments the probes are in an X and Y coordinate grid. In some embodiments the method is repeated for different stimuli.

Gress et al. shows throughout, and especially on page 609 and figure 3 a general method of assaying patterns of transcription by use of labeled total cDNA from mouse, and human cells by use of a cDNA X-Y coordinate grid array of probes spotted to form an array on a membrane. The spotted probes were cDNA clones from a library of cDNA clones. The membrane was hybridized to labeled total cDNA from different tissues. The array provides an optical signal of expression in an assayed human cell from which the labeled total cDNA is derived of the spotted cDNA, and consequently of the gene that expresses the spotted cDNA. Gress et al. shows importing the resulting data via an electrical signal of a Phosphorimager to a computer implemented relational database on page 616. Gress et al. shows in the abstract that their high density array allows for the efficient assay of thousands of clones simultaneously. Gress et al. shows on page 612 that polyA control probes hybridize non-specifically to many array cDNA probes and that other cDNA probes in the array contained repetitive sequences that also caused non-specific hybridization. Gress et al. shows on page 616 that one strategy to avoid background

non-specific hybridization is to use probes that lack polyA tails by use of modified primers. Gress et al. shows on page 602, first column, that their technique can be correlated with transcriptional, sequence, and genomic mapping information in a relational database. Gress et al. does not show subjection of assayed cells to different stimuli, or comparison of the transcriptional profile of cells that have received different stimuli, or assay of discrete portions of the complete number of genes of the cell, or use of probes with a predetermined sequence of nucleotides.

Granelli-Piperno et al. shows in figures 1-9 the effect of a variety of compounds on expression of genes of human cells. The tested compounds include cytokines, mitogens, cyclosporin A, and cycloheximide. In figures 1-4, 8, and 9 RNA samples were resolved by electrophoresis and blotted to a membrane. In figures 5-7, RNA was directly spotted as an array to a membrane. The membrane was hybridized with labeled DNA of specific genes. The response was determined by the intensity of a film image on an autoradiograph. Granelli-Piperno et al. show that assay of expression of genes after treatment of cells with drugs allows a determination of the effect of the drug on individual gene expression and further serves to gain insights on the mechanism of action of the drug.

Fodor et al.'98 shows throughout a method of making an array of polynucleotide probes of predetermined sequence by independent in situ stepwise synthesis of each oligonucleotide probe on the array. Fodor et al. '98 shows in columns 32, lines 12-24 that their arrays may be used to map the location of a molecule on a chromosomal map. Fodor et al. '98 shows in column 35 that their procedure may be used to assay the developmental stage cells from which the

assayed sample is derived. In column 78-79, Fodor et al. '98 shows that their method may be used to assay developmental stages of cells by assay of their mRNA content.

Fodor et al. '91 shows in the abstract and pages 771-772 a method of synthesizing a dinucleotide of a predetermined sequence by a photolithographic process. Fodor et al. '91 concludes on page 772 that oligonucleotide arrays that could be made by their method would be useful to detect complementary sequences in RNA and DNA, and could be used for gene mapping, fingerprinting, and diagnostics.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Gress et al. by assaying cells that have received treatments with different drugs according to the method of Granelli-Piperno et al. because Granelli-Piperno et al. shows that such an analysis serves to gain insights on the mechanism of action of the drug. The method of Gress et al. in which the treated cell cDNA is applied to an array of probes is an improvement over the assay method of Granelli-Piperno et al. in which a single gene is applied to RNA from the treated cell that is on a membrane because it allows for simultaneous assay of a large number of genes for effects of the drug on gene expression. It would have been further obvious to assay additional numbers of genes as desired to determine the effect of a drug on additional genes. Regarding the size of the probes, it would have been obvious to use portions of a cDNA probe of Gress et al. because Gress et al. shows that many array probes suffer from non-specific hybridization due to repetitive sequences of polyA tracts and that the problem may be solved by use of shorter probes. It would have been further obvious to make and use an array of probes with a predetermined sequence made by the methods disclosed by Fodor et al. '98 or Fodor et al. '91 because Fodor et al. '98 and Fodor et al. '91

show that such an array has the advantage of allowing the sequences detected in the sample to be mapped to a particular location of the genome of the organism sampled. Gress et al. also provides motivation to correlate transcription data with genomic mapping information in a relational database. Regarding the limitations of claims 71 and 72, it would be further obvious to one of skill in the art to perform simple mathematical comparisons of the levels in stimulated and control cells such as subtraction or division by the basal level to reveal the extent of change in the level of the assayed mRNA.

Claims 38, 49-51, 54, 56, 63-65, 67, 70, 80-82, and 84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gress et al. in view of Granelli-Piperno et al. in view of either Fodor et al. '98 or Fodor et al. '91 as applied to claims 38-53, 55-66, 68-83, and 85 above, and further in view of Watson et al.

The claims are drawn to assays utilizing fungal cells.

Gress et al. in view of Granelli-Piperno et al. in view of either Fodor et al. '98 or Fodor et al. '91 as applied to claims 38-53, 55-66, 68-83, and 85 above does not show assay of fungal cells.

Watson et al. shows on pages 573-575 that yeast cells contain genes that are regulated by stimuli such as metabolites.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Gress et al. in view of Granelli-Piperno et al. in view of either Fodor et al. '98 or Fodor et al. '91 as applied to claims 38-53, 55-66, 68-83, and

85 above by using yeast gene probes and cells because Watson et al. shows that yeast cells have genes that are regulated by stimuli.

(10) Response to Argument

The appellants state that Gress et al. teaches away from quantification of gene expression due to the necessity of controls, background from polyA tails and repeated sequences, and their intent to distinguish high level expression from medium levels of expression. However, Gress et al. shows that despite the necessity of controls it is possible to quantify levels of gene expression by their method, as shown in figure 2 and Table 1.

The appellants state that Granelli-Piperno et al. does not cure all the deficiencies of Gress et al. noted above, however the appellants do not appear to argue that Granelli-Piperno et al. fails to show comparison of stimulated and unstimulated cells, for which the reference is relied upon in the rejection detailed above.

The appellants argue that Fodor '91 is not combinable with Gress et al. because the use of predetermined sequences of probes shown in Fodor '91 would make Gress et al. inoperable. However the use of predetermined sequences of probes allows for use of the array of Gress et al. for additional purposes such as mapping locations of molecules, identify developmental stages of cells from which the samples are derived, and other information about the molecules that hybridize to the array, as shown in Fodor '98 and Fodor '91. The modification of the array of Gress et al. by use of predetermined sequences of probes does not conflict with the purpose of Gress et al. of using the array for identification of highly expressed cDNA clones. Arrays with probes having predetermined sequences are more versatile and useful than the array of Gress et al. because they can be used for additional purposes without preventing their use in the method

shown by Gress et al. Gress et al. states on page 609 that their method may be used to find correlations with genomic mapping information, which further indicates that Gress et al. is compatible with use of probes with predetermined sequences because probes with predetermined sequences are shown by Fodor et al. '98 to be useful for generation of chromosomal maps. The appellants state there is no motivation to combine the cited references, but the motivation to combine is discussed in the above rejection.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/John S. Brusca/

Primary Examiner

AU 1631

Conferees:

/Ram R. Shukla/

SPE 1634 & 1631

James Schultz

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SUPERVISORY PATENT EXAMINER